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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,665	11/07/2005	Donald W. Kufe	00530-108US1	6843

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EXAMINER	
FRAZIER, BARBARA S	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
10/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,665	KUFE ET AL.	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,21,22 and 48-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,21,22 and 48-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1, 2, 21, 22, and 48-67 are pending in this application.

2. Cancellation of claims 3-20 and 23-47 is acknowledged.

3. Addition of new claims 48-67 is acknowledged.

4. Claims 1, 2, 21, 22, and 48-67 are examined.

Claim Rejections - 35 USC § 112

5. The rejection of claims 1-4, 17-24, and 27-29 under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicant's amendment to claim 1.

6. The rejection of claim 27 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's cancellation of claim 27.

Claim Rejections - 35 USC § 103

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. The rejection of 19 and 20 under 35 U.S.C. 103(a) as being unpatentable over Gambacorti in view of Kumar and Kufe and further in view of Robinson et al is withdrawn in view of Applicant's cancellation of claims 19 and 20.

9. The rejection of claims 1-4, 17, 18, 21-24, and 27-29 is deemed moot in view of the new grounds of rejection, necessitated by Applicant's amendment filed 7/9/09.

10. Claims 1, 2, 22, 51, 53, 58, 62, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gambacorti-Passerini et al (WO 01/47507, hereinafter "Gambacorti") in view of Kumar et al (J.Bio.Chem., 276(20), pp. 17281-17285, 2001, hereinafter "Kumar"), Kufe et al (US Patent 7,118,862, hereinafter "Kufe"), and Fraley et al (US Patent 6,306,874, hereinafter "Fraley").

The claimed invention is drawn to a method of treating a myocardial infarction (claim 1) or a stroke (claim 51), the method comprising administering to an individual in need thereof a therapeutically effective amount of a composition comprising an N-phenyl-2-pyrimidine-amine. Applicants have elected the compound of claim 2 (also known as STI571) as the N-phenyl-2-pyrimidine amine.

Gambacorti teaches compositions of a tyrosine kinase inhibitor with an organic compound capable of binding to alpha-1-acidic glycoprotein for the treatment of proliferative diseases (e.g., tumor diseases), especially those that can be treated by inhibition of abl- receptor-tyrosine kinase activity (abstract). The preferred tyrosine kinase inhibitor is STI571 (page 4).

Gambacorti does not teach treating a myocardial infarction or a stroke with said composition.

Kumar teaches that c-Abl tyrosine kinase is activated in the response of cells to oxidative stress; said stress (from reactive oxygen species, or ROS) induces targeting of the c-Abl to mitochondria, which is associated with ROS-induced loss of mitochondrial transmembrane potential (abstract). Additionally, said c-Abl is necessary

for activation of a necrosis-like cell death (abstract) as well as apoptosis (page 17281), and thus the c-Abl kinase mediates mitochondrial dysfunction and cell death (abstract).

Kufe teaches that compounds which modulate the mitochondrial translocation of a protein (such as c-Abl) can be used to modulate levels of apoptosis, and thus can be used to treat disorders characterized by insufficient apoptosis, e.g., cancer, or excessive apoptosis (see abstract and column 5); examples of disorders associated with excessive cell death are myocardial infarction and stroke, wherein cell death occurs within and outside the central ischemic zone (col. 11, lines 41-47).

Fraley teaches that compounds used to treat tyrosine kinase dependent diseases can be used to treat the proliferation of tumor cells and may be administered to patients for use in the treatment of cancer, and may also be used to reduce or prevent tissue damage which occurs after cerebral ischemic events, such as stroke, by reducing cerebral edema, tissue damage, and reperfusion injury following ischemia (col. 19, lines 20-53).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to treat a myocardial infarction or a stroke with STI571; thus arriving at the claimed invention. One skilled in the art would be motivated to do so because administration of abl- inhibitors of tyrosine kinase activity (such as STI571) is known to treat proliferative diseases (i.e., disorders characterized by insufficient apoptosis), as taught by Gambacorti, and the inhibition of tyrosine kinase would also be reasonably expected to reduce cell death, since c-Abl tyrosine kinase activity is known to mediate cell death, as taught by Kumar. Additionally, administration of said tyrosine

kinase inhibitors is known to modulate apoptosis and therefore be useful to treat diseases characterized by excessive or insufficient apoptosis, as taught by Kufe et al, and therefore one skilled in the art would be motivated to treat myocardial infarction or stroke, disorders characterized by excessive cell death. One skilled in the art would be further motivated to use STI571 taught by Gambacorti to treat myocardial infarction or stroke, since compounds known to modulate tyrosine kinase activity are known to treat cancer as well as ischemic/reperfusion injury events such as stroke, as taught by Fraley et al. One skilled in the art would reasonably expect success from the administration of STI571 to treat myocardial infarction or stroke because Gambacorti, Kumar, Kufe and Fraley are all drawn to the problem of modulating cell death via the role of tyrosine kinase activity.

Regarding claims 2, 58, 62, and 64, Gambacorti teaches that the compound of the claims (i.e., STI571) is a preferred tyrosine kinase inhibitor (page 4).

Regarding claims 22 and 53, Gambacorti teaches that a second compound administered with STI 571 may be selected from anticoagulants (see pages 18 and 19).

11. Claims 21, 48, 49, 52, 54, 55, 57, 59, 60, 63, 65, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gambacorti in view of Kumar, Kufe, and Fraley as applied to claims 1, 2, 22, 51, 53, 58, 62, and 64 above, and further in view of Tamao et al (US Patent 5,141,947, hereinafter "Tamao").

The claimed invention is delineated above (see paragraph 10). Claims 21, 48, 49, 52, 54, 55, 57, 59, 60, 63, 65, and 66 are drawn to the above methods, wherein the

composition is co-administered in combination with a thrombolytic that is administered concurrently with, before, or after administration of the N-phenyl-2-pyrimidine-amine (see claims 21 and 52). The thrombolytic may be selected from agents such as tissue plasminogen activator (see claims 48, 49, 54, and 55).

The invention of the combined references is delineated above (see paragraph 10).

The invention of the combined references does not specifically state that the STI571 compound is co-administered with a thrombolytic.

Tamao generally teaches that thrombus is generated by fibrin formation, which may cause cerebral infarction (stroke) or myocardial infarction, and fibrin is decomposed in the process of fibrinolysis by the action of an activator. These activators are known as thrombolytic agents and include tissue plasminogen activator (p-TA), urokinase (UK), streptokinase (SK) and others (col. 1, lines 14-25).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made, when using STI571 to treat myocardial infarction or stroke according to the invention of the combined references, to co-administer a thrombolytic agent such as tissue plasminogen activator; thus arriving at the claimed invention. One skilled in the art would be motivated to do so, with a reasonable expectation of success, because the addition of a thrombolytic agent provides the benefit of decomposing the fibrin in the thrombus causing the infarction, as taught by Tamao.

Regarding claims 57, 59, 60, 63, 65, and 66, Gambacorti teaches that the compound of the claims (i.e., STI571) is a preferred tyrosine kinase inhibitor (page 4).

12. Claims 50, 56, 61, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gambacorti in view of Kumar, Kufe, and Fraley as applied to claims 1, 2, 22, 50, 51, 53, 56, 58, 61, 62, 64, and 67 above, and further in view of Stern et al (US Patent 5,426,097, hereinafter "Stern").

Claims 50, 56, 61, and 67 are drawn to the methods of claims 22 or 53, wherein the anticoagulant is heparin.

The invention of the combined references is delineated above (see paragraph 9). As stated above, Gambacorti teaches that a second compound administered with STI571 may be selected from anticoagulants (see pages 18 and 19).

The invention of the combined references does not specifically state that the anticoagulant may be heparin.

Stern generally teaches that examples of known anticoagulant agents include heparin and warfarin (col. 5, lines 26-28).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to select heparin as the anticoagulant in the composition of the combined references; thus arriving at the claimed invention. One skilled in the art would have been motivated to do so because warfarin and heparin are known anticoagulant agents in compositions for preventing thrombosis as taught by Stern, and therefore are functionally equivalent to one another. Therefore, it would be well within the purview of the skilled artisan to choose either compound as the anticoagulant of the composition of

the combined references, since the prior art establishes the functional equivalency of heparin and warfarin.

Regarding claims 61 and 67, Gambacorti teaches that the compound of the claims (i.e., STI571) is a preferred tyrosine kinase inhibitor (page 4).

Response to Arguments

13. Applicant's arguments are deemed moot in view of the new grounds of rejection, necessitated by Applicant's amendment filed 7/9/09. However, since the Examiner has retained the references of Gambacorti, Kumar and Kufe, the Examiner will respond to arguments pertaining to said references.

Applicants argue that the person of ordinary skill in the art having read Gambacorti would have had had no reason to expect that a compound (such as STI571) that induces apoptosis, would be useful in inhibiting apoptosis and treating disorders characterized by excessive oxidative stress-associated cell death.

In response to applicant's arguments against the references individually, specifically regarding Gambacorti, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue that Kumar and Kufe do not cure the deficiencies of Gambacorti. Applicants argue that nowhere does Kumar or Kufe suggest inhibiting c-

Abl kinase activity as a means of modulating oxidative stress-associated cell death. Applicants argue that the references described the importance of cellular localization of c-Abl to cell death processes, but provide no hint that inhibition of c-Abl activity may be an effective means of preventing cell death associated with oxidative stress.

This argument is not persuasive. Since Kumar teaches that c-Abl tyrosine kinase is necessary for the ROS-induced depletion of ATP and the activation of a necrosis-like cell death, and that c-Abl kinase targets to mitochondria in response to oxidative stress and thereby mediates mitochondrial dysfunction and cell death, one skilled in the art would reasonably expect that the inhibition of the activity of said c-Abl would also inhibit the mitochondrial dysfunction and resultant cell death, thereby modulating excessive cell death. Additionally, Kufe teaches that compounds that modulate the mitochondrial translocation of a protein such as c-Abl **are** expected to be useful in modulating the cell death that is associated with this translocation event (col. 11, lines 48-55), and two common disorders associated with cell death are myocardial infarction and stroke (col. 11, lines 41-47). Therefore, one skilled in the art would reasonably expect the abl-tyrosine kinase inhibitors taught by Gambacorti, such as STI571, to be useful in modulating cell death, including cell death from myocardial infarction or stroke. Furthermore, since Fraley teaches that compounds used to treat tyrosine kinase dependent diseases can be used to treat cancer as well as stroke (see rejection above), one skilled in the art would reasonably expect the tyrosine kinase inhibitors of Gambacorti, such as STI571, to also be useful in treating ischemic events, such as stroke, with a reasonable expectation of success.

Therefore, it is the Examiner's position that the claims are rendered obvious.

Conclusion

No claims are allowed at this time.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611